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(54) **IMPROVED METHOD FOR MANUFACTURING FREEZE DRIED DOSAGES IN A MULTILAMINATE BLISTER PACK**

METHODE ZUR HERSTELLUNG VON GEFRIERGETROCKNETEN DOSIERUNGEN IN EINER BLISTERPACKUNG AUS MULTILAMINAT

PROCEDE PERFECTIONNE DE PREPARATION DE DOSES LYOPHILISEES DANS UN EMBALLAGE MULTI-COUCHE ALVEOLAIRE

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Description

This invention relates generally to the field of manufacturing and dispensing pharmaceuticals, and more particularly to an improved method for manufacturing freeze dried pharmaceutical tablets in disposable single dose aluminum blister packs.

In recent years, pharmaceutical producers have turned to the use of blister packs for use in both the forming and dispensing of pharmaceutical tablets. These blister packs generally consist of a blister sheet or blister film and a lidding sheet. The blister sheet contains depressions for containing individual dosages. In a standard process for manufacturing freeze dried tablets, a single dosage, in liquid form, is introduced into each depression of the blister sheet. The blister sheet, along with the liquid dosages, is then placed into a refrigerated environment where the dosages are subjected to low temperatures to freeze them. The blister sheets are then transferred to a freeze drier, where the ice is removed by sublimation. When freeze drying is completed, the sheets are removed from the drying chamber and covered with an adhesive lidding sheet, which seals the solid dosages into their individual depressions. United States Patent No. 4,305502 is incorporated herein by reference as teaching, inter alia, a known process for manufacturing freeze dried tablets.

Blister sheets that have heretofore been used in freezing and freeze drying processes have suffered from several deficiencies. First, the blister sheets have typically been made of a polymeric substance, which, over time, can allow moisture to permeate the blister pack and reach the dosages stored inside. To solve this problem, blister sheets have been developed in which a layer of aluminum is laminated between layers of polymer. While the presence of the aluminum layer prevents moisture from permeating the blister pack, it leads to a second problem. Namely, when subjected to temperature changes during the freezing process, conventional aluminum/polymer laminates tend to curl up, due to the differences in the degree of thermal expansion or contraction of the opposing layers of the laminate. This makes their use in freezing processes difficult, since liquid product can easily spill from the formed depressions or can lie unevenly in the depressions during filling and freezing operations. Furthermore, the curling of the blister sheet can cause dosages to freeze or sublimate unevenly, since some depressions may not be in physical contact with the cold surfaces of the refrigerator or freeze drier. The only solution has been to use weights on the edges of the laminate strips to hold them sufficiently flat. Such measures are not practical in large scale manufacturing operations, and can interfere with the freezing process.

A need therefore exists for a method of utilizing a high barrier aluminum laminate in the manufacture of freeze dried dosage forms that avoids the problem of curling of the blister sheet. The present invention is therefore directed to a method for manufacturing freeze dried dosage forms in a blister pack in which liquid dosages are introduced into depressions found in a blister film and then frozen. The dosages are then freeze dried and thereafter a lidding sheet is attached to the film to seal the dosages in the depressions. According to the invention, the blister film is laminated, and comprises first and second outer layers and an impermeable intermediate layer positioned between the first and second outer layers, the first and second outer layers having substantially similar coefficients of thermal expansion. The intermediate layer is typically aluminum

The properties of the outer layers of the laminate forming the blister film in methods of the invention are such that there are no inter-layer stresses that will cause curvature of the laminate when it is subjected to temperature changes during the freeze drying process. The symmetrical response of the outer layers to such temperature changes can be achieved by using the same film material for both outer layers, or by using different materials which, by virtue of their intrinsic properties or thickness, exhibit similar degrees of thermal expansion or contraction. The outer layers can each consist of separate sublayers, as long as the sublayers in one outer layer are such that the outer layer, as a whole exhibits the same overall degree of expansion or contraction as the other outer layer.

The invention will now be described by way of example and with reference to the accompanying drawings wherein:

Figure 1 of the drawing is a plan view of a blister sheet, showing the configuration of the dosage depressions;

Figure 2 of the drawing is a transverse cross sectional view of said blister pack, taken generally along the line 2--2;

Figure 3 of the drawing is a cross sectional view of a blister sheet illustrating in further detail the relationship between the intermediate and outer layers of the blister sheet;

Figure 4 of the drawing is a cross sectional view of a blister sheet illustrating in further detail the relationship between the various layers and sublayers of the blister sheet;

Figure 5 of the drawing is a cross sectional view of a blister pack with the lidding sheet in place.

In the blister pack shown in Figure 1 and Figure 2, depressions 10 are formed in a strip 12 of the desired laminate through conventional cold forming. The size and shape of the depressions is a matter of choice that will be dictated by the size and nature of the tablet to be formed, as well as other considerations that are well known to those persons skilled in the art.

Turning to Figure 3, the laminate strip 12 comprises an intermediate layer 14 that is substantially impermeable to moisture. The preferred material for the intermedi-

ate layer is aluminum having a thickness of 10 to 100μm, with the preferred thickness being approximately 45μm, although other suitable materials may be used in its place. The intermediate aluminum layer 14 is sandwiched between a first outer layer 16 and a second outer layer 18. The outer layers may be coated or laminated onto the intermediate layer, but the layers do not necessarily have to be bonded together. The first and second outer layers are preferably made of polymeric substances, including polyamide, polyvinylchloride, polypropylene or other such substances. The first and second outer layers can be made of the same or different materials, and may have different thicknesses, as long as they have substantially similar coefficients of thermal expansion, i.e., are made of such materials and have such thickness that the first and second outer layers exhibit substantially the same degree of expansion or contraction within the plane of the film when the laminate is subjected to changes in temperature, particularly within the range of temperatures encountered during the freezing process, in which temperatures can be as low as -196°C. For instance, the laminated film 12 can consist of an intermediate layer 14 of aluminum, positioned between first and second outer layers of polypropylene 16 and 18, each layer being approximately 50μm thick.

Turning to Figure 4, it can be seen that one or both of the outer layers can also consist of separate sublayers, with each sublayer being either polymeric or non-polymeric. For instance, the first outer layer 16 can consist of two or more sublayers, such as a polyamide sublayer 20 and a polyvinylchloride sublayer 22. The second outer layer 18 can consist of a identical sublayers, or can also consist of two or more sublayers, illustrated as 24, 26 and 28, that are different than the sublayers in the first outer layer 16. Materials that may be used as sublayers include the above mentioned polymers, as well as lacquer, aluminum or paper. A priming layer can also be included. Again, the primary concern is that the first outer layer 16 and the second outer layer 18 exhibit, overall, substantially the same degree of expansion or contraction in response to temperature changes, so as to prevent curling of the blister sheet.

Returning to Figure 1, a single dosage 30 of pharmaceutical, in liquid form, is introduced into each depression in the blister sheet in a conventional manner. The blister sheet is then placed into a refrigeration unit, for instance a nitrogen spray freezing chamber, where both the sheet and the dosages are subjected to temperatures sufficient to rapidly freeze the dosages, typically as low as -196°C. Once the dosages have frozen, the blister sheet is transferred to a freeze drying chamber. Within the freeze drying chamber, the dosages are subjected to a vacuum of typically 0.1 to 1.0 mBar for a period of 180 to 500 minutes. At the same time, the temperature is steadily increased from typically about -30°C to about 60°C. As shown in Figure 5, once the dosages have been freeze dried, an adhesive lidding sheet 32 is positioned over the blister sheet, sealing the dosages into the individual depressions of the blister sheet. The procedures associated with the introduction of dosages into the blister sheet, the freezing and freeze drying of the dosages and the attachment of the lidding sheet are known to persons to skill in the art, and need not be treated in great depth herein.

Claims

1. A method for manufacturing freeze dried dosage forms in a blister pack, comprising:

   a) introducing liquid dosages into the depressions of a multilayer laminated blister film, the film comprising first and second outer layers and an impermeable intermediate layer positioned between the first and second outer layers, the first and second outer layers having substantially similar coefficients of thermal expansion;
   b) freezing the dosages;
   c) freeze drying the dosages and
   d) attaching a lidding sheet to the blister film to seal the dosages in the depressions of the blister film.

2. A method according to Claim 1 wherein the intermediate layer of the blister film is aluminum.

3. A method according to Claim 1 or Claim 2 wherein the first and second outer layers of the blister film are made of the same substances.

4. A method according to any preceding claim wherein at least one of the outer layers of the blister film is a polymeric substance.

5. A method according to Claim 4 wherein the polymeric substance comprises one or more polymers selected from the group consisting of polyethylene, polyamide, polyvinylchloride and polypropylene.

6. A method according to any preceding claim wherein the first and second outer layers of the blister film have substantially the same thickness.

7. A method according to any preceding claim wherein at least one of the outer layers of the blister film comprises a plurality of sublayers.

8. A method according to Claim 7 wherein one of the sublayers is one of a lacquer and a priming layer.

9. A method according to Claim 7 wherein one of the sublayers is a polymeric substance.

10. A method according to Claim 9 wherein the poly-

meric substance comprises one or more polymers selected from the group consisting of polyethylene, polyamide, polyvinylchloride and polypropylene.

Patentansprüche

1. Verfahren zur Herstellung gefriergetrockneter Formen von Dosiermengen in einer Durchdrückpakkung, das folgende Schritte umfaßt:

   a) Einführen von flüssigen Dosiermengen in die Vertiefungen eines mehrschichtigen laminierten Blisterfilms, wobei der Film erste und zweite äußere Lagen und eine undurchlässige, zwischen der ersten und zweiten äußeren Lage angeordnete Zwischenlage umfaßt, wobei die erste und zweite äußere Lage im wesentlichen gleiche thermische Ausdehnungskoeffizienten aufweisen;

   b) Gefrieren der Dosiermengen;

   c) Gefriertrocknen der Dosiermengen und

   d) Befestigen einer Abdeckschicht auf den Blisterfilm zum Abdichten der Dosiermengen in den Vertiefungen des Blisterfilms.

2. Verfahren gemäß Anspruch 1, dadurch gekennzeichnet, daß die Zwischenlage des Blisterfilms aus Aluminium besteht.

3. Verfahren gemäß Anspruch 1 oder Anspruch 2, dadurch gekennzeichnet, daß die erste und zweite Lage des Blisterfilms aus dem gleichen Material hergestellt sind.

4. Verfahren gemäß einem oder mehrerer der vorstehenden Ansprüche, dadurch gekennzeichnet, daß wenigstens eine der äusseren Lagen des Blisterfilms aus polymeren Materialien bestehen.

5. Verfahren gemäß Anspruch 4, dadurch gekennzeichnet, daß das polymere Material ein oder mehrere Polymere aus der Gruppe umfaßt, die aus Polyethylen, Polyamid, Polyvinylchlorid und Polypropylen besteht.

6. Verfahren gemäß einem oder mehrerer der vorstehenden Ansprüche, dadurch gekennzeichnet, daß die erste und zweite äußere Lage des Blisterfilms im wesentlichen dieselben Dicken aufweisen.

7. Verfahren gemäß einem oder mehrerer der vorstehenden Ansprüche, dadurch gekennzeichnet, daß wenigstens eine der äußeren Lagen des Blisterfilms eine Mehrzahl von Unterschichten aufweist.

8. Verfahren gemäß Anspruch 7, dadurch gekennzeichnet, daß eine der Unterschichten eine Lack- und Grundierungsschicht ist.

9. Verfahren gemäß Anspruch 7, dadurch gekennzeichnet, daß eine der Unterschichten aus polymerem Material besteht.

10. Verfahren gemäß Anspruch 9, dadurch gekennzeichnet, daß das polymere Material ein oder mehrere Polymere aus der Gruppe umfaßt, die aus Polyethylen, Polyamid, Polyvinylchlorid und Polypropylen besteht.

Revendications

1. Procédé de fabrication de doses posologiques lyophilisées sous emballage pelliculé à bulles comprenant les étapes consistant à :

   a) introduire des doses à l'état liquide dans les creux d'un film à bulles à couches laminées multiples, le film comprenant des première et seconde couches extérieures et une couche intermédiaire imperméable positionnée entre la première et la seconde couches extérieures, les première et seconde couches extérieures présentant des coefficients de dilatation thermique pratiquement identiques,
   b) congeler les doses,
   c) lyophiliser les doses, et
   d) fixer une feuille de couverture au film à bulles afin d'enfermer de façon hermétique les doses dans les creux du film à bulles.

2. Procédé selon la revendication 1, dans lequel la couche intermédiaire du film à bulles est en aluminium.

3. Procédé selon la revendication 1 ou la revendication 2, dans lequel les première et seconde couches extérieures du film à bulles sont faites des mêmes substances.

4. Procédé selon l'une quelconque des revendications précédentes, dans lequel au moins l'une des couches extérieures du film à bulles est une substance polymère.

5. Procédé selon la revendication 4, dans lequel la substance polymère comprend un ou plusieurs polymères choisis parmi le groupe constitué du polyéthylène, du polyamide, du chlorure de polyvinyle et du polypropylène.

6. Procédé selon l'une quelconque des revendications précédentes, dans lequel la première et la seconde couches extérieures du film à bulles présentent

sensiblement la même épaisseur.

7. Procédé selon l'une quelconque des revendications précédentes, dans lequel au moins l'une des couches extérieures du film à bulles comprend une pluralité de sous-couches.

8. Procédé selon la revendication 7, dans lequel l'une des sous-couches est l'une parmi une laque et une couche d'apprêt.

9. Procédé selon la revendication 7, dans lequel l'une des sous-couches est une substance polymère.

10. Procédé selon la revendication 9, dans lequel la substance polymère comprend un ou plusieurs polymères choisis parmi le groupe constitué du polyéthylène, du polyamide, du chlorure de polyvinyle et du polypropylène.

Fig. 1

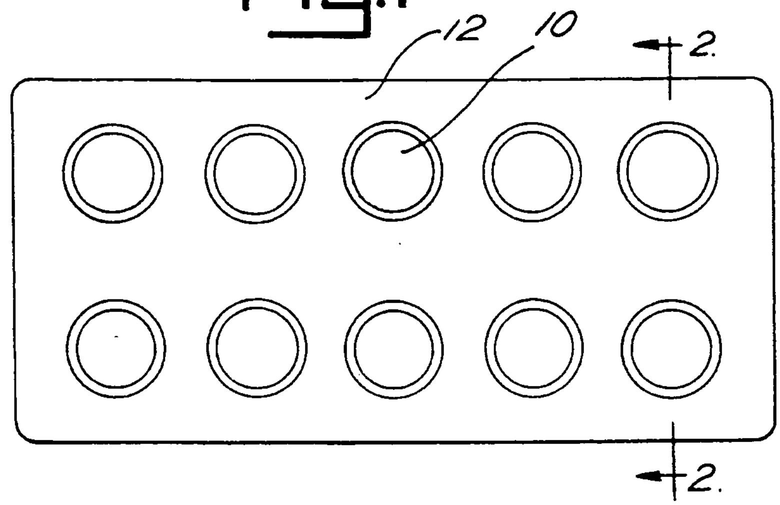

Fig. 2

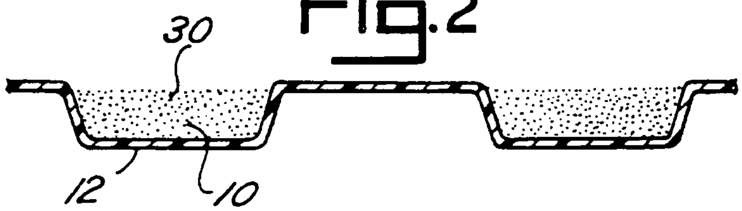

Fig. 3

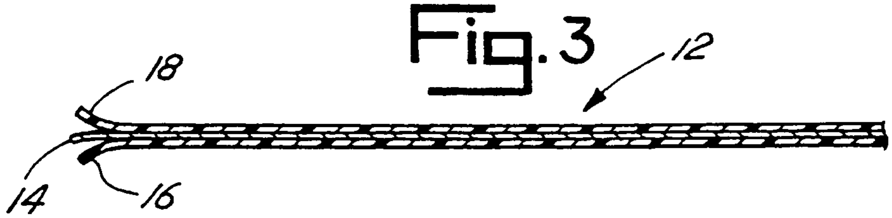

Fig. 4

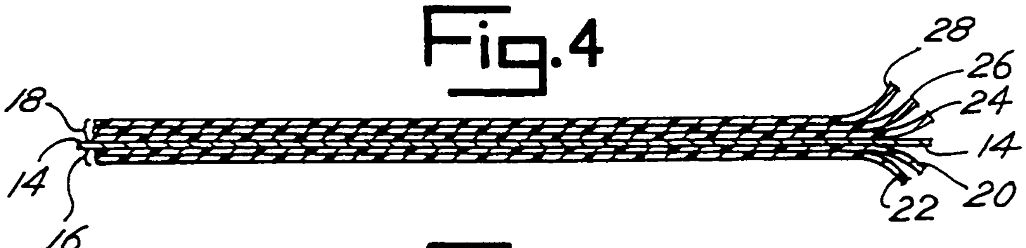

Fig. 5